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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,602	02/08/2002	Michael Toft Overgaard	07039-145001	7259

7590 11/18/2004

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,602	OVERGAARD ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-9,11,12 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-9,11,12 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response, received September 3, 2004, to the First Action on the Merits of this case, mailed April 6, 2004, is acknowledged. It is acknowledged that applicants have cancelled Claims 3-5, 10, and 13-35 and amended Claims 1, 6, and 7. Claims 1, 2, 6-9, 11, 12, and 36 are pending and are hereby reconsidered.

Claim Rejections - 35 USC § 101

Rejection of Claims 1, 2, 6-9, 11, and 12 under 35 U.S.C. § 101 for being unpatentable over Claims 1-3 and 6-10 of US Patent 6,500,630, as described in the prior action, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. (i) Claim 1 of the instant application recites a method for diagnosing a growth-promoting state by detecting PAPP-A protein while, the '630 patent recites a method for diagnosing an inflammatory condition by measuring PAPP-A. The growth-promoting condition recited in Claim 1 herein is not necessarily an inflammatory condition, as recited in Claim 1 of '630. (ii) Further, the level of PAPP-A is not necessarily measured as a level of PAPP-A protein in '630, as recited in the instant invention. (iii) A person of ordinary skill in the art would not have found it obvious to modify the method of the '630 patent to arrive at the presently claimed method.

These arguments are not found to be persuasive for the following reasons. (i) It is acknowledged that not all inflammatory conditions are growth-promoting conditions and vice versa. Thus, the recited inventions are not identical. However, for the instant rejection, the conflicting inventions need not be identical, since the rejection is not a rejection under statutory double patenting, but under the judicially created doctrine of

obviousness-type double patenting. As stated in the prior action, atherosclerosis is both an inflammatory condition and a growth-producing condition. US 6,500,630 clearly discloses that, diagnosing atherosclerosis is encompassed by the recited invention (Example 1). Likewise, the instant invention encompasses diagnosing atherosclerosis (Claim 2). Therefore, Claim 1 of US 6,500,630 renders obvious the diagnosis of atherosclerosis by measuring PAPP-A. (ii) It is acknowledged that Claim 1 of US 6,500,630 does not specifically recited measuring PAPP-A by determining the levels of PAPP-A protein. However, measuring PAPP-A protein levels would be obvious to a skilled artisan and, furthermore, is inherent in Claims 6-9 of US 6,500,630, wherein PAPP-A is detected immunologocally. (iii) Based on the claims of US 6,500,630 and teachings in the art, diagnosing atherosclerosis by measuring PAPP-A protein levels in patients and comparing those levels to the levels in a control group would be obvious to a person of ordinary skill in the art.

Therefore, rejection of Claims 1, 2, 6-9, 11, and 12 under 35 U.S.C. § 101 for being unpatentable over Claims 1-3 and 6-10 of US Patent 6,500,630, as described in the prior action, is maintained.

Claim Rejections - 35 USC § 112-First Paragraph

Rejection of Claims 1, 2, 6-9, 11, and 12 under 35 U.S.C. 112, first paragraph, for lack of enablement, as described in the prior action, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. The specification provides sufficient guidance to enable a person of ordinary skill in the art of skill in the art to practice the recited invention of diagnosing a growth-promoting state by detecting PAPP-A protein. The specification

discloses how to make and use antibodies to PAPP-A for measuring protein levels and examples of biological samples that can be analyzed for PAPP-A protein. A person of ordinary skill in the art would know which biological samples should be analyzed for determining whether an individual has a particular growth-promoting condition and which growth-promoting conditions can be diagnosed by measuring PAPP-A protein.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that, in a general way, the making and using of antibodies for detecting proteins is well known in the art. However, the prior art fails to teach which, of the extremely large number of growth-promoting states can be diagnosed by detecting PAPP-A protein. Thus, the public must look to the specification for said teaching. It is acknowledged that the specification teaches the diagnosis of atherosclerosis by measuring PAPP-A protein; however, said teaching does not enable one of skill to practice the full scope of the recited invention, a method wherein any growth-promoting state can be diagnosed by measuring PAPP-A protein. In fact, the specification teaches away from diagnosing cancer by measuring PAPP-A mRNA or protein (Fig 4). Likewise, because the prior art fails to teach which of the extremely large number of tissues can be successfully used for diagnosis of any specific growth-promoting state by measuring PAPP-A protein in the tissue, one of skill must look to the specification. Although the specification teaches diagnosis of atherosclerosis by measuring PAPP-A protein in the β-actin cells from the coronary media, the plaque, and the media of the vasa vasorum of necroscopy samples, said limiting teaching fails to enable one to know which of the essentially unlimited types of tissues should be examined for PAPP-A protein in order to diagnosis any specific growth-promoting state. For example, would analysis of PAPP-A

levels in blood successfully diagnose wound healing and, if so, how would one differentiate a diagnosis of wound healing from a diagnosis of atherosclerosis?

For these reasons, and those discussed in the First Action on the Merits, rejection of Claims 1, 2, 6-9, 11, and 12 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 1, 2, 6, 8, 9, 11, and 12 under 35 U.S.C. 103(a) as being unpatentable over Jacot et al, 1998 in view of Bersinger et al, 1984, as evidenced by Lawrence et al, 1999 (IDS), for the reasons described in the prior action, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments. (i) The cited references fail to provide a reasonable expectation of success in diagnosing a growth-promoting condition by measuring PAPP-A levels. The findings in Jacot et al do not prove a causal link between degradation of IGFBP-4 and smooth muscle cell proliferation. (ii) Bersinger et al teaches away from measuring PAPP-A levels to screen for a growth-promoting condition, since a change in PAPP-A protein was not detected in association with ovulation. (iii) Further, Jacot et al and Lawrence et al teach that IGF-I activity is regulated by protein besides IGFBP-4.

These arguments are not found to be persuasive for the following reasons. (i) Jacot et al clearly state that, "In summary, we conclude that high glucose concentrations

are modulating IGFBP-4 proteolysis through an effect on protease levels". Therefore, one of skill would expect success in detecting elevated PAPP-A protein as a diagnosis for hyperglycemic conditions, as well as atherosclerosis, which has been clearly linked to hyperglycemia (Kirpichinikov et al, 2001). (ii) It is acknowledged that Bersinger et al did not detect elevated PAPP-A levels in association with any specific phase of the ovulatory cycle; not all growth-promoting states can be diagnosed by measuring PAPP-A protein. However, Jacot et al teach that, IGFBP-4 proteolysis by PAPP-A is increased upon incubation with conditioned medium derived from smooth muscle cells treated under hyperglycemic conditions. Thus, one of skill in the art would predicted that, more likely than not, levels of PAPP-A are increased in hyperglycemic, growth-inducing conditions (also see (i) above). (iii) The fact that IGFBP-4 protease (PAPP-P) levels are expected to reflect a growth-promoting condition, specifically atherosclerosis, is the important point of the instant invention. The fact that IGF-I activity may be regulated by proteins besides IGFBP-4, would not alter the diagnostic importance of measuring PAPP-A levels.

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bersinger et al, 1984 in view of Epstein et al, 1992, Harlow and Lane, 1988, and Oxvig et al, 1993. As described in the prior action, Bersinger et al teach a method for detecting PAPP-A protein using an antibody. Bersinger et al do not teach the use of an antibody specific for PAPP-A but not the PAPP-A/major basic protein (MBP) complex. Epstein et al teach the purification of antibodies using a method of reverse immunoaffinity purification comprising "...adsorbing unwanted antibodies to antigen(s) coupled to a solid phase (usually chromatography beads) and either eluting the remaining antibodies over the

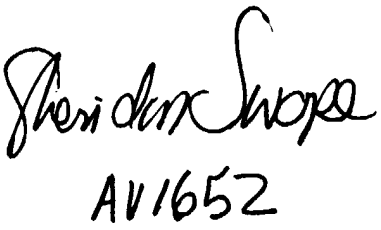
coupled antigen or removing the beads by centrifugation" (pg 10436, parg 3, lines 1-5). It would have been obvious to a person of ordinary skill in the art to use the method of Epstein et al to link the PAPP-A/MBP complex to a resin, pass polyclonal antibodies directed to said complex as well as free PAPP-A over the resin, and collect the flow-through that contains the PAPP-A-specific antibodies, which bind to the free PAPP-A but do not bind to the PAPP-A/MBP complex. In addition, based on standard teachings in the art, one could further purify the desired antibodies using a resin linked with free PAPP-A wherein, the flow-through from the first PAPP-A/MBP-linked resin could be passed through the free PAPP-A-linked resin and the antibodies bound to this latter resin eluted to prepare purified antibodies that bind only to free PAPP-A and not the PAPP-A/MBP complex (Harlow and Lane, 1988). The suggestion to make said antibodies comes from Oxvig et al wherein they state that, commercially available polyclonal anti-PAPP-A is polyspecific, also reacting with MBP (Abstract). Thus, one of skill would be motivated to make, using the reverse immunoaffinity purification method of Epstein et al, antibodies that are specific for PAPP-A vs the PAPP-A/MBP complex. Furthermore, one of skill would be motivated to use said purified antibodies to detect PAPP-A because they would not recognize the PAPP-A/MBP complex. The expectation of success is high, as the preparation of specific antibodies by reverse immunoaffinity purification and their use for immunodetection of proteins is well known in the art. Therefore, Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bersinger et al, 1984 in view of Epstein et al, 1992 and Oxvig etal, 1993.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan Lee Swope, Ph.D.



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